REMARKS

Claims 1-17 are pending in the application.

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1-17 under U.S.C. 103(a) as being unpatentable over U.S. Patent 6,849,749 to Petersen, U.S. Patent 6,753,433 to Hilden et al. and/or Japanese Patent Publication 2002-114,770 to Eikoku et al. (mistakely identified by the Examiner as Gao et al.) in view of U.S. Patent 5,087,638 to Belanger.

The Examiner contends that Petersen discloses aroylation of a substituted phthalide with a halophenyl Grignard reagent in dichloromethane in a manner described by the Applicants. The Examiner specifically referenced column 8, lines 16-36 of Petersen. Applicants disagree with the Examiner's contention.

The Grignard reaction of Petersen and the Applicants differ in at least the solvent in which the reaction is carried out. Applicants conduct a Grignard reaction in a co-solvent system (page 4, lines 10-11). Specifically, "the co-solvent is an aliphatic or aromatic chlorinated solvent or an aromatic hydrocarbon ... selected from methylene dichloride, ethylene dichloride, trichloroethane, carbon tetrachloride, chloroform, chlorobenezene, dichlorobenzene, and mixtures thereof ... [and] [a]s [to] hydrocarbon co-solvents, toluene, benzene or xylene, or mixtures thereof" (see paragraph [0025] of the Published Patent Application 2006/01116522). Petersen dicloses preparing a 4-fluorobromobenzene Grignard reagent "in dry THF" (column 8, line 20), then adding the Grignard reagent dropwise to a suspension of 5-N,N-dimethylcarbamylphthalid "in dry THF" (column 8, line 22). In other words, Petersen discloses conducting the Grignard reaction in dry THF and not in a co-solvent as required by the process of independent claims 1 and 17 of the instant invention.

Additionally, Applicants' co-solvent system provides for a greater yield of a purer 5-substituted-1-(4-fluorophyenyl)-1,3-dihydroisobenzofuran (see Tables 1 and 2, below)

than the processes of the cited art, which use a single solvent synthetic route. Applicants submit that at least one of a purer product and a greater yield would not be predicted by an individual of ordinary skill in the art based on the disclosures of the cited prior art.

Applicants further submit the higher purity level provides at least one source of

TABLE 1

Sl. No	Sub-phthalide	Solvent mixture	5-Bromo-phthalane purity by HPLC	Yield
1	(5-bromo-phthalide)	*Tetrahydrofuran (THF)	80.5%	56%
2		THF: Methylene dichloride	92.5%	69.3%
3		THF: Ethylene dichloride	86.5%	65%
4		THF: Chloroform	92.2%	72.9%
5		THF: Toluene	82.5%	58.3%
6		THF: Chlorobenzene	78.5%	58.3%
7		THF: Benzene	82.5%	58.3%

*Prior art process

TABLE 2

Sl. No	Sub-phthalide	Solvent mixture	5-Cyano-phthalane purity by HPLC	Yield
1	(5-cyano-phthalide)	*Tetrahydrofuran (THF)	95.6%	29%
2		THF: Methylene dichloride	99.32%	86%
3		THF: Ethylene dichloride	99.12%	85.0%
4		THF: Chloroform	99.35%	86.5%
5		THF: Toluene	97.5%	70%
6		THF: Chlorobenzene	94.2%	78%
7		THF: Benzene	93.5%	78%

*Prior art process

supporting rationale for patentability, specifically: "[p]ure materials are novel *vis-á-vis* less pure or impure materials because there is a difference between pure and impure materials" (MPEP 2144.04 VII). The 5-bromophthalane prepared by the co-solvent system of the present invention has a purity level as high as 92.5%. That is, 5-bromophthalane prepared in a co-solvent of the subject invention is purer by as much as 12.5% (in absolute percentage terms) than 5-bromophthalane prepared in a single solvent process of the prior art. Additionally, the purer 5-bromophthalane prepared by the subject invention is obtained in greater yield, in some instances greater by as much as 13% (in absolute percentage terms). That is, Applicants' synthetic process is more efficient and less wasteful than the prior art synthetic processes.

Similarly, the 5-cyanophthalane prepared by the co-solvent synthetic process of Applicants had a purity level of 95.4% having a 3.8% greater purity level than that of the prior art single solvent process (in absolute percentage terms). Purer 5-cyanophthalane prepared by Applicants' co-solvent process is also obtained in greater yield, by as much as 57% (in absolute percentage terms) or a 200% increase in yield in relative terms (29% yield for prior art process, compared to 86% yield for the subject invention process).

Moreover, the synthetic processes recited in pending Claim 1 differ from the synthetic processes of the prior art in the molar equivalents of sodium borohydride. The process of the Applicants utilizes 0.5 molar equivalents of sodium borohydride. The prior art processes utilize an excess of sodium borohydride, see for example Belanger et

al., which utilizes 2.0 molar equivalents of sodium borohydride. Applicants submit that this reduction in the amount of sodium borohydride is distinct from the art cited by the Examiner and that such a reduction in the amount of sodium borohydride is not obvious in view of that art.

The Examiner further contends Petersen discloses conducting the Grignard reaction in dichloromethane (page 2, line 5 of last paragraph). Applicants respectfully submit that Petersen discloses *extracting* the reaction product with dichloromethane after the THF solvent is removed following the quenching of the reaction mixture with ice water (column 8, lines 33-36). Petersen does not disclose utilizing dichloromethane as a co-solvent for the Grignard reaction as the Examiner contends.

The Examiner additionally contends that Hilden et al. discloses an aroylation process using dichlorobenzene as solvent for a Grignard reaction. In particular, the Examiner references column 5, lines 1- 61, to support his contention that Hilden et al. disclose the use of a halogenated solvent in a synthetic route to 2-cholormethyl-4-cyano-benzoyl chloride, specifically the section where Hilden et al. disclose: a dihalide compound comprising a halogenated-methylene and a haloketone (column 4, line 66 to page 5, line 49) which is further reacted with a Grignard reagent.

The Grignard reactants of Applicants' invention differ from those of Hilden et al. at least in that Applicants react a 4-fluorophenylmagnesium halide with 5-substituted phthalide, while Hilden et al. disclose reacting the 4-fluorophylmagnesium halide with 2-cholormethyl-4-cyano-benzoyl chloride. More specifically, Applicants react the Grignard reagent with the ketone group of the phthalide lactone ring to form 4-substitued-2-hyroxymethyl-4'-flurobenzophenone, while Hilden et al. disclose reacting the Grignard reagent with a non-cyclic haloketone to form 3-chloromethyl-4-(4-fluoro-benzoyl)-benzonitrile. In other words, the synthetic process of Applicants' and the synthetic process disclosed by Hilden et al. differ in at least the Grignard reactants. Applicants react a 5-substituted phthalide, while Hilden et al. disclose reacting a 2-cholormethyl-4-cyano-benzoyl chloride, *not a phthalide, much less a 5-substitued cyclic phthalide*.

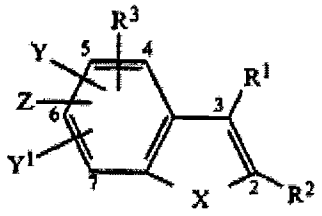
Additionally, Applicants' synthetic route differs from those of Hilden et al. in at least that, Hilden el al. do not diclose a reduction of 4-substituted-2-hydroxymethyl-4'-fluorobenzophenone ketone group, and/or a cyclization reaction of a 4-substituted-2-hyroxymethylphynyl-1-(4-flurophyenyl) methanol to form a 5-substituted-1-(4-fluorophyenyl)-1,3-dihydroisobenzofuran, as employed with Applicants' synthetic route.

Applicants disagree with the Examiner's contention that Hilden et al. discloses the use of dichlorobenzene as a co-solvent. Hilden et al. prepare 2-chloromethyl-4-cyano-benzoyl chloride in dichlorobenzene (column 5, line 34) and isolated the 2-chloromethyl-4-cyano-benzoyl chloride therefrom (column 5, lines 50-56). Within the art, isolation of a compound from a solvent, such as dichlorobenzene, means that the compound is separated from the dichlorobenzene by at least crystallization and/or distillation. Following the isolation and purification, the 2-chloromethyl-4-cyano-benzoyl chloride is reacted with a Grignard reagent in an inert organic solvent. Hilden et al. disclose suitable inert organic solvents to be "toluene, xylene, or commonly used ethers such as tetrahydrofuran, diethyl ether, di-n-butylether, tetrabutylmethyl ether, ethylene glycol dimethyl ether, 1,4-diioxane or mixtures thereof" (see column 6, lines 22-26). In other words, Hilden et al. do not disclose dichlorobenzene as a suitable solvent and/or co-solvent for a Grignard reaction.

The Examiner cites the abstract of Eikoku et al. as disclosing an "analogous process using benzene." But the Eikoku et al. abstract does not mention benzene as a solvent and/or co-solvent for a synthetic process comprising a 4-fluorophenyl magnesium halide Grignard reagent. The synthetic route disclosed by Eikoku et al. starts with 2',6'-dicarboxyphenyl-(4-fluorobenzophenone). In other words, Eikoku et al. do not disclose a synthetic step for incorporating a 4-fluorophenyl entity, since their synthetic route starts with the 4-fluorophyenyl entity incorporated. More specifically, Eikoku et al. disclose a method of condensing the para-carboxylic acid phenyl group with the ketone entity of the fluorobenzophenone to form 6-carboxy-3-(4'-fluorophenyl) phthalide. Thereafter, reacting a 3-(dimethylamino) propylmagnesium halide Grignard reagent with the 6-carboxy-3-(4'-fluorophenyl) phthalide to form citalopram. In other words, Eikoku et al. and Applicants differ in at least that, Applicants' synthetic route comprises: a) the addition of a 4-fluorophyenyl entity by reacting a 4-fluorophyenyl Grignard reagent with

the ketone entity of a 5-member cyclic lactone to form 4-substitued-2-hyroxymethyl-4'-flurobenzophenone; b) a ketone reduction of a 4-substituted-2-hydroxymethyl-4'-fluorobenzophenone; and c) a cyclization reaction of a 4-substituted-2-hyroxymethylphynyl-1-(4-flurophyenyl) methanol to form a 5-substituted-1-(4-fluorophyenyl)-1,3-dihydroisobenzofuran.

The Examiner further submits that the above teachings of Petersen, Hilden et al., and/or Eikoku et al. in view of Belanger et al. supports an obviousness rejection under 35 USC § 103(a) of claims 1-17. Specifically, the Examiner contends that Applicants' invention would have been obvious to one of ordinary skill in art when Petersen, Hilden et al. and/or Eikoku et al. are taken in view of the teachings of column 19, lines 1-56 of Belange et al. Applicants disagree with the Examiner's contentions on this point. Applicants submit that, the combination of Belanger et al. with one or more of Petersen, Hilden et al. and/or Eikoku et al. is improper. Belanger et al. is explicitly directed to compounds of Formula I (see column 2, lines 54-65 of Belanger et al.).



(Formula I)

Formula I is not chemically or structurally representative of the compounds disclosed by one or more of the Applicants, Petersen, Hilden et al. and/or Eikoku et al. Specifically, the 5-membered ring of Formula I is not representative of the lactone group of citalopram. Formula I differs from the 5-member lactone group of citalopram in at least the following: a) Formula I contains a double bond between the carbons 2 and 3, while citalopram does not; b) Formula I lacks a ketone group, citalopram contains a ketone group; and c) Formula I has a heteroatom at position 1, citalopram has a heteroatom at position 2. Furthermore, Formula I is not representative of the formulae I-VI of Petersen, formulae I-IV of Hilden et al., compounds I-XIV of Eikoku et al. and formulae 1-5 of Applicants disclosure. Singularly or combined, Petersen, Hilden et al. and/or Eikoku et

al. fail to explicitly anticipate and/or impliedly suggest structures representative of Formula I of Belanger et al. Similarly, Belanger et al. fail to explicitly anticipate and/or impliedly suggest the structures of the Applicants, Petersen, Hilden et al. and/or Eikoku et al.

Furthermore, the aroylation reaction of Scheme IV (column 19, lines 1-56 of Belanger et al.) referenced by the Examiner is to a Friedel-Crafts aroylation reaction, catalyzed by aluminum chloride, not a Grignard reaction comprising magnesium halide as the Examiner argues. The Friedel-Crafts and Grignard reactions have long been considered separate and distinct reactions. The Friedel-Crafts reaction is typically an electrophillic aromatic substitution reaction, while the Grignard reaction is typically a nucleophilic addition reaction. Those of ordinary skill in the art would not expect the teachings related to an electrophillic aromatic substitution reaction catalyzed by aluminum chloride to be applicable to nucleophilic addition reaction involving an organometallic magnesium halide complex. Therefore, it is improper for the Examiner to combine Belanger et al. with one or more of Petersen, Hilden et al. and/or Eikoku et al. and/or to consider Belanger et al. germane to teachings of Applicants' disclosure.

Applicants respectfully submit that the claims are in allowable form. Additionally, Applicants respectfully submit that the claims are not anticipated by the cited art and that the claims are non-obvious to one of ordinary skill in the art when Petersen, Hilden et al. and/or Eikoku et al. are taken in view of Belange et al.

Based at least on the foregoing, the Applicants believe that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,
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